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10/007,047	12/06/2001	Theodora Ross	UM-06692	6232

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EXAMINER
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FETTEROLF, BRANDON J

ART UNIT	PAPER NUMBER
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1642

MAIL DATE	DELIVERY MODE
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01/29/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

**Advisory Action  
Before the Filing of an Appeal Brief**

Application No.

10/007,047

Applicant(s)

ROSS ET AL.

Examiner

Brandon J. Fetterolf, PhD

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**--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

THE REPLY FILED 21 December 2006 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.  
b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**NOTICE OF APPEAL**

2. ☐ The Notice of Appeal was filed on \_\_\_\_\_. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

**AMENDMENTS**

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because  
(a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);  
(b) ☐ They raise the issue of new matter (see NOTE below);  
(c) ☒ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or  
(d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: \_\_\_\_\_. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).  
5. ☐ Applicant's reply has overcome the following rejection(s): \_\_\_\_\_.  
6. ☐ Newly proposed or amended claim(s) \_\_\_\_\_ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).  
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.  
The status of the claim(s) is (or will be) as follows:  
Claim(s) allowed: \_\_\_\_\_.  
Claim(s) objected to: \_\_\_\_\_.  
Claim(s) rejected: 24-27, 29, 36 and 95.  
Claim(s) withdrawn from consideration: 84-86 and 91-93.

**AFFIDAVIT OR OTHER EVIDENCE**

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).  
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).  
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

**REQUEST FOR RECONSIDERATION/OTHER**

11. ☐ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: \_\_\_\_\_.  
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). \_\_\_\_\_.  
13. ☐ Other: \_\_\_\_\_.

***Response to Amendment***

The Amendment filed on 12/21/2006 in response to the previous Final Office Action (10/18/2006) is acknowledged, but has not been entered. The amendment has not been entered because the recited limitation of "chance" of recurrence in the proposed amendment has not been previously considered. As such, the proposed amendment would require further consideration and search of the prior art.

Claims 24-27, 29, 36, 84-86, 91-93 and 95 are currently pending.

Claims 84-86 and 91-93 are withdrawn from consideration as being drawn to a non-elected invention.

Claims 24-27, 29, 36 and 95 are currently under consideration.

**The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.**

**Rejections Maintained:**

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 24-27, 29, 36 and 95 **remain** rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of characterizing prostate cancer in a patient already diagnosed with prostate cancer by detecting the presence or absence of HIP1 in a sample with a nucleic acid probe configured to hybridize to a HIP1 nucleic acid sequence consisting of the nucleic acid sequence of SEQ ID NO: 1, wherein the absence of HIP1 in said sample is indicative of PSA non-recurrence and/or recurrence free survival, does not reasonably provide enablement for a method of characterizing prostate cancer in a patient already diagnosed with prostate cancer by detecting the presence or absence of HIP1 in a sample with a nucleic acid probe configured to hybridize to a HIP1 nucleic acid sequence consisting of the nucleic acid sequence of SEQ ID NO: 1, wherein the absence or presence of HIP1 is indicative the stage of said cancer. The specification

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does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized in *re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988). The court in *Wands* states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.'" (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the nature of the invention, (2) the relative skill of those in the art, (3) the breadth of the claims, (4) the amount or direction or guidance presented, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the state of the prior art, and (8) the predictability or unpredictability of the art.

Although the quantity of experimentation alone is not dispositive in a determination of whether the required experimentation is undue, this factor does play a central role. For example, a very limited quantity of experimentation may be undue in a fledgling art that is unpredictable where no guidance or working examples are provided in the specification and prior art, whereas the same amount of experimentation may not be undue when viewed in light of some guidance or a working example or the experimentation required is in a predictable established art. Conversely, a large quantity of experimentation would require a correspondingly greater quantum of guidance, predictability and skill in the art to overcome classification as undue experimentation. In *Wands*, the determination that undue experimentation was not required to make the claimed invention was based primarily on the nature of the art, and the probability that the required experimentation would result in successfully obtaining the claimed invention. (*Wands*, 8 USPQ2d 1406) Thus, a combination of factors which, when viewed together, would provide an artisan of ordinary skill in the art with an expectation of successfully obtaining the claimed invention with additional experimentation would preclude the classification of that experimentation as undue. A combination of *Wands* factors, which provide a very low likelihood of successfully obtaining the claimed

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invention with additional experimentation, however, would render the additional experimentation undue.

**The nature of the invention**

The claims are drawn to a method of characterizing prostate cancer in a subject diagnosed with prostate cancer comprising detecting the presence or absence of HIP1 with a nucleic acid probe configured to hybridize to a HIP1 nucleic acid sequence consisting of the nucleic acid sequence of SEQ ID NO: 1. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001).

**Level of skill in the art**

The level of skill in the art is deemed to be high, generally that of a PhD or MD.

**The breadth of the claims**

Applicants broadly claim, in part, a method of characterizing prostate cancer in a patient already diagnosed with prostate cancer by detecting the presence or absence of HIP1 in a sample with a nucleic acid probe configured to hybridize to a HIP1 nucleic acid sequence consisting of the nucleic acid sequence of SEQ ID NO: 1, wherein the absence or presence of HIP1 is indicative the stage of said cancer. The claims are further drawn to said "stage" of cancer is selected from the group consisting of high-grade prostatic intraepithelial neoplasia, benign prostatic hyperplasia, prostate carcinoma and metastatic prostate carcinoma.

**Guidance in the specification and Working Examples**

The specification teaches (page 4, lines 9-12) that HIP1 may be utilized in a method for characterizing prostate tissue in a subject, wherein the presence or absence of HIP1 characterizes the tissue sample. For example, the specification teaches that HIP1 expression in individual patients reveals that there were progressively higher frequencies of HIP1 expression in benign, PIN, PCA and metastatic case. Conversely, there were progressively lower frequencies of the lack of HIP1 expression among the same (page 65, lines 25-28 and Figure 4a). Moreover, the specification teaches the clinical implications associated with HIP1 expression, wherein patients with tumors

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which did not stain for HIP1 expression did not develop a PSA recurrence (page 66, lines 5-11 and page 67, Table 1). In addition, the specification teaches that there is a survival advantage of PCa patients with tumors that had no HIP1 expression, wherein all patients that lacked HIP1 expression survived 67 months without evidence of recurrence as compared to 28% of the patients whose tumors expressed HIP1 died of prostate cancer (page 66, lines 17-26 and Figure 4b). Thus, while the specification teaches that in some instances there is a correlation between HIP1 expression and prostate cancer, the specification does not appear to provide a nexus between the presence or absence of HIP1 in prostate tissues and the patients risk of prostate specific antigen failure, the risk of prostate cancer metastasizing, the risk of prostate cancer reoccurring or assessing the state of prostate cancer. For example, while the specification (page 65, lines 28-31) teaches the presence of HIP1 expression correlated with the ordinal categories of benign vs. PIN vs. PCa vs. Metastatic, the specification appears to be silent on an "amount" of HIP1 which can be used to differentiate the stage of cancer because the results shown in Figure 4a shows the frequency (% cases) of HIP1 expression and not a differentiating amount.

#### *Quantity of experimentation*

The quantity of experimentation in the areas of cancer diagnosis and/or characterizing a particular stage of cancer is extremely large given that what may be "preferable" in the lab is only suggestive and does not qualify as a reasonable expectation of success, especially in a highly unpredictable art such as determining the a particular stage of cancer.

#### *The unpredictability of the art and the state of the prior art*

The state of the art at the time of filing was such that one of skill could recognize that the expression of a cancer-associated nucleic acid molecule that appears to be 60% identical to the instantly claimed nucleic acid of SEQ ID NO: 1 has been found to be associated with colon cancer (see Chen et al. US 6,794,501, of record). With regards to HIP1 and/or a nucleic acid sequence consisting of SEQ ID NO: 1, the prior art appears to be silent an association of HIP1 and/or a nucleic acid consisting of SEQ ID NO: 1 and prostate cancer, and further, HIP1 being an identifier of a particular stage of prostate cancer.

It is noted, as stated above, that the specification (page 65, lines 28-31) teaches the presence of HIP1 expression correlated with the ordinal categories of benign vs. PIN vs. PCa vs. Metastatic. However, the specification appears to be silent on an "amount" of HIP1 which can be used to differentiate the stage of cancer because the results shown in Figure 4a shows the frequency (% cases) of HIP1 expression and not a differentiating amount. Therefore, the teachings above do not clearly indicate whether or not HIP1 is indicative of the cancerous state in prostate cells. In other words, what may be "preferable" in the lab is only suggestive and does not qualify as a reasonable expectation of success, especially in a highly unpredictable art such as determining the stage of prostate cancer. For example, Tockman *et al* (Cancer Res., 1992, 52:2711s-2718s, *of record*) teach considerations necessary in bringing a cancer biomarker (intermediate end point marker) to successful clinical application. Although, the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to other oncogenic disorders such as prostate cancer. Tockman *et al* teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and **if validated** (emphasis added) can be used for population screening (p. 2713s, col. 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and *link* those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). In addition, Slamon et al. (Science Vol. 235, January 1987, pages 177-182, *of record*) teach other essential factors that are known to be important in the prognosis of breast cancer in individual patients such as size of the primary tumor, stage of the disease at diagnosis, hormonal receptor status, and number of axillary lymph nodes

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involved with disease (page 178, 1<sup>st</sup> column, 2<sup>nd</sup> paragraph). Such data are critical to assessing actuarial curves for relapse (Figure 3), and for comparing disease-free survival and overall survival to prognostic factors (Table 4).

### Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the lack of guidance provided in the specification for correlation in vitro results to in vivo success, and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as written.

In response to this rejection, Applicants assert that the claims have been amended to include the elements of the absence of HIP1 binding indicative of PSA recurrence or recurrence free survival. Accordingly, Applicants submit that the presently claimed invention is enabled.

As Applicant's arguments appear to be solely drawn to the amended claims which have not been entered, such arguments have not been considered.

Therefore, No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.



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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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